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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/811,410	03/20/2001	Rudi Scherhag	0480/01227	1484

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EXAMINER	
SNEDDEN, SHERIDAN	
ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 08/27/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/811,410	SCHERHAG ET AL.	
	Examiner	Art Unit	
	Sheridan K Snedden	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-11 is/are pending in the application.

4a) Of the above claim(s) none is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-11 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 9 and 10 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's amendment of claims 4, 6, 7, 10 11 and 12 is acknowledged.

Information Disclosure Statement

The information disclosure statements filed 20 March 2001 and 25 January 2002 fail to comply with 37 CFR 1.98(a)(3).

Specification

The spacing of the lines of the specification is such as to make reading and entry of amendments difficult. New application papers with lines double spaced on good quality paper are required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4-5 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. An anticoagulant that has a terminal half-life of at least 4 hours (claim 4) is critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). In In re Wands, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure

meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

- the nature of the invention,
- the state of the prior art,
- the predictability or lack thereof in the art,
- the amount of direction or guidance present,
- the presence or absence of working examples,
- the breadth of the claims,
- the quantity of experimentation needed, and
- the level of the skill in the art.

Breadth of the claims and Nature of the Invention

In the instant case, the invention claims a method of the prophylactic treatment to a patient who has undergone extracorporeal circulation utilizing an anticoagulant with a terminal half-life of 4 hours. The specification teaches the use of heparin, hirudin, conjugated PEG-hirudin and hirudin derivates as the anticoagulants that may be used in the above method.

Amount of Direction or Guidance Present and State of the Prior Art

The specification discloses the peptides of heparin, hirudin, conjugated PEG-hirudin and hirudin derivates. The identification of these compounds are consistent with the state of the prior art. With regards to the half-life of the above compounds, the state of the prior art is exemplified by the teachings of Bischoff, who teaches the half-life of hirudin as 1 hour (column 1, line 24) and the half life or the longest lasting PEG-hirudin conjugate as more than 3 hour (column 10, line 55).

Level of the Skill in the Art and Presence or Absence of Working Examples

The specification fails to provide guidance to one of ordinary skill in the art of how to obtain a derivate of hirudin that has a terminal half-life of 4 hours. Table 4 provides an example

of how the half-life is calculated, but the example summarized in Table 4 fails for link the results with an actual compound.

Predictability or Lack thereof in the Art

Additional PEG-hirudin conjugates or hirudin derivates with a half-life of at least 4 hours cannot be predicted.

Quantity of Experimentation Needed

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. It is the specification, not the knowledge of one skill in the art that must supply the novel aspects of an invention in order to constitute adequate enablement. Due to the current state and level of skill in the art, the unpredictability of obtaining a hirudin compound with a terminal half life of at least 4 hour, and lack of guidance provided for in the specification, the invention is not enabled without undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 3 and dependent claims thereto are indefinite as the claims refers to an effective amount but do not indicate what the effective amount is to do nor what specific complication is the effective amount is to treat. Note that simply administering, as is claimed,

does not per se nor necessarily result in a successful treatment, thus the claim would appear to be incomplete.

Claim 4 is indefinite as to the use of "at least about" because it is unclear whether the limitation should read "a least 4" or "about 4." See same issue in claim 11.

Claim 5 is indefinite because it is unclear as to what activity is referred to by "enduring pharmacodynamic activity" as recited in the claim.

Claim 6 is unclear as to when PEG-hirudin is administered. The claim appears to be incomplete as it is not clear if PEG-hirudin is to be administered in conjunction with an anticoagulant agent or is to be administered in as the anticoagulant agent or represents an additional step to the method. Please note that for clarity, "PEG" should be spelled out in full at first use in an independent or dependent claim.

Claim 10 is rejected for the use of "APTT." Please note that for clarity, "APTT" should be spelled out in full at first use in an independent or dependent claim.

Claim 11 is indefinite as "any of claims 8 to 10" should read as "any one of" for clarity of dependence.

Claims 2 and 7-11 are indefinite in that they depend on claim 1 and do not clarify the ambiguity.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 and 6-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Bucha *et al.* (DE 199 15 862 A1; see also Derwent Acc-No: 2000-665999). Bucha *et al.* teach the administration of a polyethylene glycol-hirudin (PEG-hirudin) conjugate (claim 6) as an anticoagulant for the prophylaxis of thrombogenic effects, which may lead to vascular complications after treatment, in a patient being treated extracorporeal kidney replacement therapy, such as a patient suffering form chronic renal insufficiency (see Bucha *et al.*, Example 4; see claims 1-3, 6 and 7 of the instant application). Bucha *et al.* specifically teach the treatment of chronic glomerulonephritis requiring regular hemodialysis (see claim 7 of the instant application). The PEG-hirudin was administered to the patient as a bolus, a single dose, at the start of hemodialysis (see claim 9 of the instant application). Bucha *et al.* teach that PEG-hirudin was administered as a single dose per hemodialysis (see claim 8 of the instant application). Thus, the reference anticipates claims 1-3 and 6-9 of the instant application.

Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by De Rosa *et al.* (US Patent 5,723,576). De Rosa *et al.* teach hirudin as an anticoagulant and antithrombotic agent (column 2, lines 4-5) useful for therapeutic, prophylactic and diagnostic applications. De Rosa *et al.* specifically teach the use of hirudin, and derivative compounds thereof, in the prophylaxis of vascular complication such as arterial thrombosis (claims 2 and 3), and specifically teach the use of the above compounds in extracorporeal circulation, particularly hemodialysis (column 7, lines 49-57). De Rosa *et al.* teach that the above compounds can be

administered to a patient with the effective amount of 0.05 mg/kg to 250 mg/kg patient body weight per day (column 7, lines 19-37; see claims 1 and 3 of the instant application).

As a whole, De Rosa teach a method for the prophylactic treatment of vascular complications (arterial thrombosis) of a subject undergoing extracorporeal circulation comprising the administration of an effective amount (0.05 mg/kg to 250 mg/kg patient body weight per day) of an anticoagulant (hirudin). Thus, the reference anticipates claims 1-3 of the invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bucha *et al.* (DE 199 15 862 A1; see also Derwent Acc-No: 2000-665999) in further view of Bischoff (US Patent No: 5,362,858). Bucha *et al.* teach the administration of PEG-hirudin (claim 6) as an anticoagulant for the prophylaxis of thrombogenic effects, which may lead to vascular complications after treatment, in a patient being treated extracorporeal kidney replacement therapy, such as a patient suffering form chronic renal insufficiency (see Bucha *et al.*, Example 4; see claims 1-3, 6 and 7 of the instant application). Bucha *et al.* specifically teach the treatment of chronic glomerulonephritis requiring regular hemodialysis (see claim 7 of the instant application). The PEG-hirudin was administered to the patient as a bolus, a single dose, at the

start of hemodialysis (see claim 9 of the instant application). Bucha *et al.* teach that PEG-hirudin was administered as a single dose per hemodialysis (see claim 8 of the instant application). Bucha *et al.* does not teach that the PEG-hirudin conjugate used in the treatment above had a half-life of about 4 hours or possessed an "enduring pharmacodynamic activity."

However, Bischoff teaches a polyethylene glycol-hirudin (PEG-hirudin) conjugate and derivates thereof (abstract; column 3 lines 18-20). Bischoff teaches a PEG-hirudin compound that has a half-life of more than three hours (column 10, line 55). This teaching by Bischoff addresses the limitation in claim 4, which recites an agent with a half-life of about 4 hours. The PEG-hirudin conjugate has a significantly longer half-life as compared to the non-conjugated form, hirudin (column 10, lines 42-62). As such, the PEG-hirudin conjugate has an "enduring pharmacodynamic activity" as recited in claim 5 of the instant application.

Together, Bucha *et al.* and Bischoff teach a method for the prophylactic treatment of vascular complications of a subject undergoing extracorporeal circulation comprising the administration of an effective amount of the anticoagulant, PEG-hirudin with a half-life of about 4 hours. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to substitute the PEG-hirudin conjugate taught by Bischoff in the method of treatment taught by Bucha *et al.* above because the two conjugates are made from the same source material and are both known in the art as a more stable form of hirudin. The person of ordinary skill in the art would have been motivated to use the PEG-hirudin taught by Bischoff, and expected success, because the PEG-hirudin the has a half-life of about 4 hours (claim 4) which gives the compound a an "enduring pharmacodynamic activity" (Bischoff; claim 5).

Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bucha *et al.* as applied to claims 1-6 above, and further in view of De Rosa *et al.* (US Patent 5,723,576). Bucha *et al.* specifically teach the treatment of chronic glomerulonephritis requiring regular hemodialysis (see Bucha *et al.*, Example 4; see claim 7 of the instant application). The PEG-hirudin was administered to the patient as a bolus, a single dose, at the start of hemodialysis (see claim 9 of the instant application). Bucha *et al.* teach that PEG-hirudin was administered as a single dose per hemodialysis (see claim 8 of the instant application). Bucha *et al.* does not teach the effect of the dosing regime on APTT measurement.

De Rosa *et al.* teach that administration of the anticoagulant hirudin derivates prolong APTT 250%, or 2.5 fold (column 10, line 60). De Rosa *et al.* teach the use of hirudin derivatives as an anticoagulant and antithrombotic agents (column 2, lines 4-5) useful for therapeutic, prophylactic and diagnostic applications. De Rosa *et al.* specifically teach the use of hirudin derivative compounds, in the prophylaxis of vascular complication such as arterial thrombosis, and specifically teach the use of the above compounds in extracorporeal circulation, particularly hemodialysis (column 7, lines 49-57). De Rosa *et al.* teach that the above compounds can be administered to a patient with the effective amount of 0.05 mg/kg to 250 mg/kg patient body weight per day (column 7, lines 19-37).

Together, Bucha *et al.* and De Rosa *et al.* teach a modified method for the prophylactic treatment of vascular complications of a subject undergoing extracorporeal circulation

comprising the administration of an effective amount of the anticoagulant, a method utilizing hirudin derivates capable of prolonging APTT by 2.5 fold. Additionally, as taught by Bucha *et al.*, the anticoagulant hirudin derivates may be administered as a single dose per hemodialysis for multiple doses (see claims 8, 10 and 11 of the instant application). The person of ordinary skill in the art would have been motivated to use the hirudin derivatives taught by De Rosa *et al.*, and expected success, because hirudin derivatives taught by De Rosa *et al.* are known to prolong APTT 250% and have been utilized in a method of the prophylactic treatment of vascular complication in a subject who has undergone extracorporeal circulation. Prolonging APTT by 250% or 2.5 fold addresses the limitations of claims 10 and 11, which recite 2.7 to 1.8 fold and at least 1.2 fold, respectively. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan K Snedden whose telephone number is (703) 305-4843. The examiner can normally be reached on Monday - Friday, 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 746-3975 for regular communications and (703) 746-3975 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

SKS
August 22, 2002

SKS

Christopher S. F. Low

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